CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

MEDICAL REVIEW(S)

JAN 27 2000

MEDICAL OFFICER'S REVIEW OF AMENDMENTS 024 AND 033
FINAL REPORTS FOR THE U.S. CLINICAL TRIALS INDUCING ABORTION UP TO 63 DAYS GESTATIONAL AGE AND COMPLETE RESPONSES REGARDING DISTRIBUTION SYSTEM AND PHASE 4 COMMITMENTS

NDA Number: 20-687

Applicant: Population Council
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Date Review Finalized: November 22,1999

I. General Information:

A. Name of Drug:
1. Established Name: Mifepristone
2. Trade Name: None designated as yet.

3. Laboratory Code Name: RU 38486 (RU-486).

B. Pharmacologic Category: Antiprogestational and antiglucocorticoid agent.

C. Proposed Indication: Medical termination of intrauterine pregnancy through 49 days' pregnancy.

D. Dosage Form and Route of Administration: Tablet for oral administration.

E. Strength: Each tablet contains 200 mg of mifepristone.

F. Dosage: Three 200 mg tablets (600 mg) of mifepristone are taken as a single oral dose. Unless abortion has occurred, the patient takes two 200 μg tablets (400 μg) of misoprostol orally two days after ingesting mifepristone.

G. Related Drugs: None marketed.

H. Table of Contents:

II. Manufacturing Controls: Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics: Please refer to pharmacologist's review for details.

IV. Clinical Background:

Mifepristone is a synthetic steroid that was approved for the termination of pregnancy in France in December 1988 (launched September 1989), in Sweden in 1992, in the United Kingdom in 1991, and in China in 1988. (It should be noted that mifepristone used in China is not manufactured by Roussel Uclaf but by domestic companies). When administered alone in total doses of 1400-1600 mg over 1-10 days, the success rate was 64-85%. Subsequent studies demonstrated that the administration of mifepristone followed by a synthetic prostaglandin analog increases the success rate to over 95%. In a preliminary study of 100 women, the success rate of 600 mg mifepristone and 0.2 mg misoprostol was 95% for pregnancies of no more than 49 days of amenorrhea. Misoprostol is a synthetic prostaglandin E_1 analog [redacted] In the [redacted] misoprostol [redacted]

Nine phase 2 clinical studies to determine the most effective dose and dosage regimen for mifepristone used alone for the interruption of pregnancy were conducted in France between 1983 and 1986. Patients in these studies were entered with a target gestational age of less than or equal to 41 days of amenorrhea. One thousand patients were exposed to doses ranging from 100 mg for one to four days to 800 mg for one day.

Following completion of the phase 2 studies, nine phase 3 clinical trials employing a single 600 mg dose of mifepristone were conducted to evaluate the efficacy and the

safety of this dose. The target population was patients with pregnancies having a gestational age ≤42 days of amenorrhea. A total of 2,459 patients were studied.

The advantage of combining mifepristone 600 mg with a prostaglandin (sulprostone 250μg I.M. 36-48 hours later) for pregnancy interruption was demonstrated in 1985. A series of ten clinical trials were conducted between 1987 and 1991 to confirm and extend these initial observations. In addition to sulprostone, other prostaglandins including gemeprost, 15MePGF 2a, and prostine E_2 were evaluated. During the ten studies, a total of 19,947 patients were exposed to mifepristone administered as a single 600 mg dose. One of these studies enrolled over 16,000 patients. Very rare cases of hypotension and one myocardial infarction were reported. Successful termination of early pregnancy was achieved in 82.6 to 100% of the patients enrolled in these studies and the safety of mifepristone was confirmed.

The efficacy and safety of mifepristone given as a single 600 mg oral dose in combination with misoprostol 0.4 mg orally administered approximately 36 to 48 hours after mifepristone for termination of pregnancy was evaluated in two historically controlled, pivotal clinical trials conducted in France. The first study included women with intrauterine pregnancies of ≤ 49 days and the second study included women with intrauterine pregnancies of ≤63 days. In the second study, a second dose of 200 μg of misoprostal was given 3 hours after the first dose if complete abortion had not occurred. In the first study of 1205 evaluable patients, the complete abortion rate was 95.4% and in the second study of 1104 evaluable patients, the complete abortion rate was 92.8%. These two studies were evaluated in the review of a new drug application that was submitted March 16, 1996.

V. Regulatory Background:

2 **Page(s) Redacted**

Deliberative Process

VI. Statistical Consultation: None required

VII. Clinical Studies:

The efficacy and safety of mifepristone was evaluated in two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols (166A and 166B) at 17 centers (University hospitals, Planned Parenthood clinics, and free-standing clinics). The studies were conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

Data from the two studies were combined in the following evaluation.

A. Investigators:

Dr. Paul Blumenthal	Baltimore, Maryland
Dr. Lynn Borgatta	White Plains, New York
Dr. Mitchell Crenin	Pittsburgh, Pennsylvania
Dr. Catherine Dean	St. Louis, Missouri
Dr. Susan Haskell	Des Moines, Iowa
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Dr. Eugene Rothenberg	Shrewsbury, New Jersey
Dr. Katherine Sheehan	San Diego, California
Dr. Laszlo Sogor	Cleveland, Ohio
Dr. Judith Tyson	Burlington, Vermont
Dr. Peter Vargas	Aurora, Colorado
Dr. Carolyn Westhoff	New York, New York

B. Objectives of the Study:

The study was conducted to evaluate the effectiveness, safety, acceptability, and feasibility of using mifepristone and misoprotol in a variety of clinical settings within the United States health care system for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

C. Rationale for the Study:

Extensive experience has been gained outside the United States with the use of mifepristone and various prostaglandin analogs, including misoprostol, for the termination of pregnancies up to 63 days, with complete abortion rates ranging from 92.7% to 99%. The applicant wished to confirm the efficacy and safety of the regimen in the United States.

D. Method of Assignment to Treatment:

Eligible patients fulfilling all of the inclusion criteria and none of the exclusion criteria were assigned to one of the three treatment groups, based on gestational age.

E. Number of Subjects:

A total of 2,121 patients were enrolled including 859 patients in groups 1,722 patients in group 2, and 540 patients in group 3.

F. Duration of Clinical Trial:

Patients were to receive mifepristone on day 1 and misoprostol on day 3 and were to be observed in the clinical setting for at least 4 hours after misoprostol administration. Patients were to return for evaluation on day 15.

G. Inclusion Criteria:

1. Was at least 18 years of age and in good general health.

2. Requested a voluntary termination of pregnancy.

3. Had a positive urine pregnancy test.

4. Had an intrauterine pregnancy with a duration of amenorrhea of ≤63 days (from the first day of her last menstrual period) that was confirmed by uterine size on pelvic examination and by vaginal ultrasound evaluation.

5. Agreed to have a surgical termination of pregnancy if the study procedures failed to terminate her pregnancy.

6. Was a resident of the United States.

7. Gave written informed consent to participate in the study and was willing and able to participate.

H. Exclusion Criteria:

1. Had evidence of any disorder which represented a contraindication to the use of mifepristone (such as adrenal disease or a condition requiring chronic corticosteroid administration) or misoprostol (such as asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or a known allergy to prostaglandins).

2. Had a history of severe liver, respiratory, or renal disease or thromboembolism.

3. Had a cardiovascular disease, e.g. angina, valve disease, arrhythmia, cardiac failure, or insulin dependent diabetes.

4. Had hypertension that was being treated on a chronic basis or had blood pressure of greater than 140/90mmHg.

5. Was anemic (hemoglobin < 10 g/dL or hematocrit < 30%).

6. Had a known clotting defect or was receiving anticoagulants.

7. Had an IUD *in situ*.

8. Was breastfeeding.

9. Had adnexal masses or tenderness on pelvic examination that suggested pelvic inflammatory disease.

10. Had an ectopic pregnancy or threatened abortion.

11. Was over 35 years of age and smoked more than 10 cigarettes per day, and

had another risk factor for cardiovascular disease such as diabetes mellitus, hyperlipidemia, hypertension, or a family history of ischemic heart disease.

12. Was unlikely to understand and comply with the requirements of the study.

13. Lived or worked more than one hour from the emergency care facility that served the abortion center.

I. Trial Period:

September 13, 1994 to September 12, 1995

J. Dosage and Mode of Administration:

Patients were not to eat during the one hour before and after the administration of mifepristone. In the presence of the investigator, each patient was administered three 200 mg mifepristone tablets by mouth with no more than 240 mL of water. Patients were informed that they should not smoke during the 48 hours following mifepristone administration and on the day misoprostol was to be administered. Unless the investigator could verify unequivocally that complete abortion had occurred, patients were administered two 200 μg misoprostol tablets by mouth with no more than 240 mL of water in the presence of the investigator 36 to 60 hours after the administration of mifepristone.

K. Efficacy Assessments:

Pelvic examinations were performed before mifepristone administration at visit 1, before misoprostol administration at visit 2, during the 4 hour observation period after misoprostol administration, and at the visit 3 evaluation. At visit 1, patients also had transvaginal ultrasound examinations and quantitative hCG β subunit pregnancy tests performed. At visits 2 and 3, ultrasound examinations were performed at the discretion of the investigator.

The outcome of treatment was classified as follows:

1. Complete abortion: pregnancy termination and complete expulsion of the products of conception without the need of surgical intervention.

2. Incomplete abortion: pregnancy termination with either partial expulsion or nonexpulsion of the products of conception diagnosed at visit 3 or at study end if later than visit 3 with surgery required.

3. Ongoing pregnancy: a viable pregnancy diagnosed at visit 3 based on fetal heartbeat and/or fetal growth indicating gestations that are

two weeks older than at visit 1; surgery required.

4. Medical intervention: before visit 3, the investigator judged that a surgical intervention was medically indicated.

5. Patient request: before visit 3, the patient chose not to proceed with the medical method of abortion and requested surgical intervention.

In the analyses of treatment outcome, complete abortion only was classified as a treatment success. All other categories resulted in a surgical procedure and , therefore, were classified as treatment failures.

L. Safety Assessments:

Adverse events were summarized and evaluated.

M. Disposition of Patients:

A total of 2121 patients were enrolled. Of these, 2015 (95.0%) were included in the efficacy analyses. There were 106 patients excluded from the efficacy analyses because of failure to show up for visit 3, thus preventing confirmation of a final outcome. For 92 of these patients, there was some information suggesting a successful outcome. For one excluded patient, there was evidence that suggested failure. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. All 2121 patients were evaluable for safety. A total of 827 patients in Group 1, 678 patients in Group 2, and 510 patients in Group 3 were included in the efficacy evaluation.

N. Demographic Characteristics:

Most patients were Caucasian (71%), 20-29 years of age (61%; mean age of 26.9 years), of normal body mass index (71%), nulliparous (55%) and had a previous elective abortion (51%). The differences among the three gestational age groups in race distribution and mean age, weight, and body mass index were small and not of clinical significance.

O. Results:

1. Efficacy:

Success and failure rates are summarized in Table 1.

Table 1
(Sponsor's Table 4.1)
Treatment Outcomes by Gestational Age (Evaluable Patients)

Treatment Outcomes	Group 1 ≤ 49 days N = 827	Group 2 50-56 days N = 678	Group 3 57-63 days N = 510
Total Successes	762 (92%)	563 (83%)	395 (77%)
RU-486 alone	40 (5%)	12 (2%)	4 (< 1%)
Plus misoprostol	722 (87%)	551 (81%)	391 (77%)
Total Failures	65 (8%)	115 (17%)	115 (23%)
Med intervention	13 (2%)	26 (4%)	21 (4%)
Patient request	5 (< 1%)	13 (2%)	12 (2%)
Incomplete ab	39 (5%)	51 (8%)	36 (7%)
Ongoing preg	8 (< 1%)	25 (4%)	46 (9%)

Failures are discussed in this review in the "Safety" section of "Results."

Complete abortion rates according to time of occurrence are displayed in Table 2 as confirmed by the investigators.

Table 2
(Sponsor's Table 5.1)
Time to Occurrence of Complete Abortion

Occurrence Time	Group 1 ≤ 49 days N =827	Group 2 50-56 days N=678	Group 3 57-63 days N=510
Mifepristone alone	40 (4.8%)	12 (1.8%)	4 (0.8%)
≤ 4h after misoprostol	376 (45.5%)	312 (46.0%)	178 (34.9%)
> 4h & < end of day 4	178 (21.5%)	118 (17.4%)	118 (23.1%)
After day 4	168 (20.3%)	121 (17.8%)	95 (18.6%)
Surgical intervention	65 (7.9%)	115 (17.0%)	115 (22.5%)

2. Safety:

Adverse events, regardless of causality, were reported for at least 99% of the patients in each gestational age group. More than one adverse event was reported for most patients. The majority of adverse events were of mild or moderate severity. Approximately 23% of the adverse events in each gestational age group were judged to be severe. The most common adverse event was abdominal pain, including uterine cramping. This was to be expected since the treatment procedure is designed to induce the uterine cramping (and bleeding) necessary to produce an abortion.

Other commonly reported adverse events were nausea, vomiting, headache, diarrhea, and dizziness. No serious adverse events were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. Table 3 shows that the rates of most, but not all, adverse events that occurred in patients whose gestational age was ≤ 49 days were not significantly different from the rates across all gestational age groups.

Table 3

Most Commonly Reported Adverse Events

Adverse Event	Group 1 ≤ 49 days N=859 Percentage	Groups 1, 2, and 3 ≤ 63 days N=2121 Percentage
Abdominal pain (cramping)	96	97
Nausea	61	67
Headache	31	32
Vomiting	26	34
Diarrhea	20	23
Dizziness	12	12
Fatigue	10	9
Back pain	9	9
Uterine hemorrhage	5	7
Fever	4	4
Viral infections	4	4
Vaginitis	3	4
Rigors (chills/shaking)	3	3
Dyspepsia	3	3
Insomnia	3	2
Asthenia	2	2
Leg pain	2	2
Anxiety	2	2
Anemia	2	2
Leukorrhea	2	2
Sinusitis	2	2
Syncope	1	2

Table 4 shows the rates of adverse events in any gestational age group which were significantly different across gestational age groups.

Table 4
Adverse Events Significantly Different Across Gestational Age Groups

Adverse Event	Group 1 ≤ 49 days Percentage	Group 2 50-56 days Percentage	Group 3 57-63 days Percentage
Nausea	61	71	72
Vomiting	26	38	41
Diarrhea	20	23	26
Uterine hemorrhage	5	8	10

No patient was discontinued from the study because of an adverse event and there were no deaths.

The median bleeding duration for group 1 was 14 days and 15 days for groups 2 and 3.

The proportions of patients who received any medications for bleeding increased with increasing gestational age form 5.7% in group 1 to 10.7% in group 3. A total of 146 patients (6.9%) received uterotonics (ergot-type medications or oxytocin) for bleeding.

Fourteen patients (0.7%) were hospitalized for an adverse event. Of these patients, 2 of 4 in the ≤ 49 days group, 3 of 5 in the 50-56 days group, and 3 of 5 in the 56-63 days group had adverse events (severe excessive bleeding) which were considered to be study drug related. The other patients were hospitalized for reasons unrelated to study treatment (pneumonia, meningitis, automobile accident, depression, shooting injury, endometritis).

Nineteen patients (0.9%) had emergency room visits that did not result in hospitalization. Sixteen of these 19 patients had excessive bleeding (2, ≤ 49 days; 7, 50-56 days; 7, 57-63 days). The other three visits were for chest pain, nausea and vomiting, and cramping.

Four patients received blood transfusions (1, ≤ 49 days; 2, 50-56 days; 1, 57-63 days). Three of these patients were hospitalized.

IV fluids were administered for various reasons to 9 (1.0%) patients in the ≤ 49 days group, 19 (2.6%) in the 50-56 days group, and 18 (3.3%) in the 57-63 days group.

The following five potentially serious adverse events occurred:

A 34 year old patient with a 20 year history of seizures and a pregnancy of

46 days gestational age had a mild seizure (convulsion) on the day of mifepristone administration and received 250 mg of dilantin. In the opinion of the investigator, the patient's seizure was not related to treatment with mifepristone and she received misoprostol 47 hours after the mifepristone.

A 28 year old of 54 days gestational age with a negative gastrointestinal history reported possible blood in her stool a month after misoprostol administration. In the opinion of the investigator, the patient's melena was not related to study treatment.

A 23 year old of 57 days gestational age developed moderate purpura (body bruises) that lasted for one day without treatment ten days after receiving misoprostol. In the opinion of the investigator, the patient's purpura was not related to study treatment.

A 21 year old of 57 days gestational age developed severe viral meningitis 6 days after receiving misoprostol and was hospitalized. In the opinion of the investigator, the patient's meningitis was not related to study treatment.

A 27 year old of 60 days gestational age with a negative gastrointestinal history reported blood in her stool 3 days after receiving misoprostol. At the time of last contact with the patient three weeks later, no further incidents of melena had been reported. In the opinion of the investigator, the patient's melena was not related to study treatment.

The proportions of patients with a decrease in hemoglobin or hematocrit of more than 20% from their pre-mifepristone administration levels increased significantly with increasing gestational age, from 3.1% in the ≤ 49 days group to 8.0% in the 57-63 days group.

Of the 1028 patients with hemoglobin measurements before and after misoprostol administration, 131 had a decrease of at least 2mg/dL (7.8%, ≤49 days; 15.0%, 50-60 days; 17.4% 57-63 days).

Hypotension after administration of misoprostol occurred in 0.3% - 1.4% of all treated patients.

Hypertension after administration of misoprostol occurred in 1.5% - 1.7% of all treated patients.

Decrease in heart rate by > 20% after administration of misoprostol occurred in 18.2% - 21.3% of all patients.

Increase in heart rate by >20% after administration of misoprostol occurred in 11.8% - 14.1% of all patients.

For the subgroup of patients with a full panel of laboratory tests, the median changes were small and not of clinical significance.

Failure of the mifepristone - misoprostol procedure required surgical intervention which is an additional safety concern, albeit small. A total of 295 patients were classified as having failed medical abortion. Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure. In group 1 (≤ 49 days gestation), of the 65 failures, 8 (12%) patients had ongoing pregnancies, 39 (60%) patients had incomplete abortions, 5 (8%) requested and had surgical terminations performed, and the remaining 13 (20%) patients had surgical terminations directly related to the medical procedure. The failure rates for medical intervention, patient request, incomplete abortion, and ongoing pregnancy were significantly higher in groups 2 and 3 than in group 1.

For each gestational age group, the adverse event rates were highest at Planned Parenthood clinics and lowest at Free-Standing clinics, with university hospital clinics in the middle.

VIII. Reviewer's Comments, Evaluation, and Conclusions:

Two studies were conducted according to two identical protocols at 17 centers to evaluate a mifepristone - misoprostol regimen for the termination of pregnancies in the United States health care system. The studies included patients in three gestational age groups:

Group 1: amenorrhea of ≤ 49 days
Group 2: amenorrhea of 50-56 days
Group 3: amenorrhea of 57-63 days

The studies included women who requested a voluntary termination of pregnancy, had a positive pregnancy test, and a documented intrauterine pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than ten cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adrenal masses, had

ectopic pregnancies, or had signs or symptoms suggesting that they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. A total of 2,121 women were enrolled in the two studies including 859 women who were in the ≤ 49 days group, which is the gestational age which is the subject of this application.

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography and women were assigned to the appropriate gestational age group.

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took three 200 mg tablets of mifepristone orally in the presence of the investigator. Patients did not eat for one hour before and after the consumption of the mifepristone. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. Patients did not smoke during the 48 hours following mifepristone consumption and on the day misoprostol was administered. Patients then remained at the clinics under observation for at least four hours. Adverse events such as nausea, vomiting, diarrhea, abdominal pain, and vaginal bleeding were rated by the women and recorded. Blood pressure and heart rate were measured at least hourly. Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 as "spotting", "normal", or "heavy." During this period, the women were also monitored for the expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a vacuum aspiration or dilatation and curettage constituted a failure. A surgical procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to followup; 5 had continuing pregnancies when last seen at visit 2. The efficacy analysis, therefore, included 2015 women. No additional information is available on the outcomes of the 5 women with continuing pregnancies who were lost to followup. All other women with continuing pregnancies were aborted surgically.

Efficacy was 92% in the ≤ 49 days group with a lower 95% confidence interval of 90%. This is somewhat less than the 95.5% efficacy with a lower 95% C.I. of 94.2% reported in the pivotal French studies upon which approval of this application was recommended.

Efficacy was 83% in the 50-56 days group with a lower 95% confidence interval of 80%. Efficacy was 77% in the 57-63 days group with a lower 95% confidence interval of 74%.

The 92% success rate in the ≤ 49 days group is an acceptable one.

The median duration of bleeding in the ≤ 49 days group was 14 days. The average duration of bleeding was 16 days. This is considerably longer than the average duration of 9 days reported in the French studies upon which approval of this application was recommended, but is an acceptable duration.

Excessive bleeding necessitated blood transfusion in only 1 patient in the ≤ 49 days group and required hospitalization of only 2 patients in the ≤ 49 days group. An additional 2 patients in the ≤ 49 days group were treated in the emergency room for excessive bleeding. Thirteen (2%) patients in the ≤ 49 days group required surgical intervention because of excessive bleeding. Bleeding was managed by the administration of uterotonic agents such as oxytocin, methylergonovine or vasopressin in 5% of patients in the≤ 49 days group.

The adverse event rates were higher in these studies than those in the pivotal French studies upon which approval of this application was recommended. This is shown in Table 5.

Table 5

Frequent Adverse Events (≤ 49 days) in French and U.S. Trials

Adverse Event	French Trials	U.S. Trials
Abdominal pain (cramping)	83%	96%
Nausea	43%	61%
Headache	2%	31%
Vomiting	18%	26%
Diarrhea	12%	20%
Dizziness	1%	12%

The majority of adverse events were of mild or moderate severity. The difference in the frequency of common adverse events noted above is acceptable.

In the pivotal French trials, 5.5% of subjects had a decrease in hemoglobin of greater than 2g/dL while in the U.S. trials, 7.8 % of patients in the ≤ 49 days group had such a decrease. This difference is an acceptable one.

The U.S. clinical trials confirmed the findings of the pivotal French trials that mifepristone and misoprostol are safe and effective in terminating pregnancies of up to 49 days gestation even though the success rate in the U.S. trials was lower

than that of the French trials. This lower success rate might be related to the lack of experience of most of the U.S. investigators with medical abortion. The lower success rate might also be attributable somewhat to the fact that in the U.S. trials, a woman's request for a surgical termination any time after receiving mifepristone was honored and classified as a failure rather than being excluded form the efficacy analysis. However, in the ≤ 49 days group, less than 8% of the failures (5 patients) were because of patient requests.

The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age. The majority of surgical interventions were for incomplete abortion and excessive bleeding.

This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.

Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility including at least a four hours stay after the administration of the misoprostol.

In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects).

In the U.S. clinical trials, an increase in the incidence of some adverse events (vomiting, nausea, diarrhea, uterine hemorrhage) occurred in the 50-56 and 57-63 days gestational age groups compared to the ≤ 49 days group. The safety profile of the ≤ 49 days group in the U.S. study did not differ significantly from the pivotal French studies, even though the incidence of common adverse events in the U.S. clinical trials was higher than that of the French trials in the ≤ 49 days group. The percentage of patients in the U.S. studies and the French studies requiring hospitalization, requiring blood transfusion and experiencing heavy bleeding was about the same. However, about 1.6% of the patients in the ≤ 49 days group in the U.S. study had surgical intervention because of heavy bleeding compared to less than 1% of patients in the French studies. The average duration of bleeding was 16 days in the U.S. studies compared to 9 days in the French studies.

While the U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical

abortions with gestations of 49 days duration or less, they demonstrate that with longer durations of gestation (50-56 days and 57-63 days), the treatment regimen is less effective and the incidence of adverse events is higher.

A comparison of medical termination of pregnancy with surgical termination is of interest in a polulation of women who are given a choice to select between medical and surgical termination of early pregnancy. Such a comparative clinical trial was conducted according to a uniform protocol from 1991 to 1993 in urban clinics in China, Cuba, and India, three countries where abortion is legal and available. A total of 1373 women with amenorrhea ≤ 56 days were given a choice of surgical abortion or mifepristone and misoprostol in the same dosage regimen as used in the U.S. studies. The results of this study were published in 1997. The medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India). In each site failure rates of medical abortion increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients. The only serious complication was excessive bleeding in medical abortion patients, which is a reason for surgical intervention and for dissatisfaction among medical abortion patients. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients. Slightly higher proportions of medical than surgical patients were dissatisfied (8.8% versus 3.8%). Despite the bleeding pattern and the failure rate of the medical abortion method, particularly in China, medical abortion by the mifepristone and misoprostol regimen was said by the authors of this published study to be safe, efficacious, and highly desired by and acceptable to women in developing countries.

The results of a smaller study published in 1999 comparing mifepristone to surgical abortion in U.S. women are consistent with the findings of the larger comparative clinical trial done in China, Cuba, and India. The study was a nonconcurrent, prospective, cohort analysis of 178 mifepristone - misoprostol and 199 suction curettage abortion subjects with intrauterine pregnancies ≤ 63 days gestational age. The medical abortion cohort represents all of the subjects enrolled at one U.S. clinical site for the mifepristone clinical trial between December, 1994 and August, 1995. The surgical abortion cohort was enrolled prospectively at the same clinical site between November, 1995 and December, 1996. Overall, 18.3% of medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (R.R. 3.93; 95% CI 1.87,8.29). The risk of failure demonstrated a statistically significant upward trend from 3.3 to 4.4 with advancing gestational age. Four mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine

mifepristone patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4). Mifepristone patients reported significantly longer bleeding in all three gestational age groups. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients. The use of antiemetic agents during the abortion procedure was significantly more common in mifepristone patients than surgical patients (31.1% versus 1%). Mifepristone patients were routinely offered oral narcotics for expulsion-related pain, and 78.5% used them. Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients (RR 7.4, 95% CI 4.7, 11.5). Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients (0.6%) (RR 117.9, 95% CI 16.7, 834.7).

Although the mifepristone and surgical abortion techniques are both safe and effective, the abortion and post-abortion experiences differ significantly as reported in the two published studies above that permit direct comparison of the two techniques in a prospective manner.

IX. Labeling Evaluation:

Comments regarding labeling revisions were transmitted to the sponsor in a letter dated September 18, 1996. Revised draft labeling was submitted by the sponsor June 25, 1999 and currently is under review.

X. Conclusion:

The results of the U.S. studies do not adversely differ significantly from the results of the two pivotal French clinical trials which were the basis for the approvable letter to the sponsor September 18, 1996.

XI. Recommended Phase 4 Studies:

The medical officer, in his revised original NDA review, recommended that phase 4 studies with the following objectives be conducted:

A. To monitor the adequacy of the distribution and credentialing

system.

B. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.

C. To assess the long-term effects of multiple use of the regimen.

D. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

E. To study the safety and efficacy of the regimen in women (1) under
18 years of age, (2) over age 35, and (3) who smoke.

F. To ascertain the effect of the regimen on children born after treatment failure.

The phase 4 recommendations were included in the approvable letter to the sponsor dated September 18, 1999.

XII. Consideration of Advisory Committee Members' Comments:

Part of the review process for this application included seeking expert advice from members of the FDA Reproductive Health Drugs Advisory Committee at a public meeting July 19, 1996. The committee voted 6-0 (with two abstentions) that the pivotal studies (French studies) presented at that time showed that the benefits of a mifepristone and misoprostol regimen for terminating early pregnancies outweighed its risks. The studies presented to the committee involved women treated within 49 days of the beginning of their last menstrual period.

Preliminary safety data from recently completed U.S. trials were also presented.

The committee recommended some phase 4 studies and individual committee members offered some individual comments for consideration by the FDA staff, particularly comments regarding labeling and the drug distribution system. All comments were carefully and fully considered and, to the extent possible, implemented.

The applicant was asked September 18, 1996 to submit a comprehensive description of the proposed distribution system. The following complete response from the applicant was submitted to FDA August 18, 1999 regarding the distribution system:

"The details of the distribution system for the product are in the process of being worked out with the proposed distributor. However, the following key principles will be adhered to in the final distribution arrangements:

- Product will only be available from one or two distributors nationwide and not through retail pharmacies or direct to physicians from the manufacturer.

- Each physician interested in obtaining the product must request the product from the distributors, register with them and open an account.

- Access to the distributors will be through the distributors' general order system and through a specially established toll free telephone number with product ordering as an option.

- Aside from standard credit checks run by the distributors to open a new account, each requesting physician will be required to register by providing their BNDD # and their state Medical License #, and signing a letter that they have the following:

  - The ability to accurately confirm the duration of pregnancy

  - The ability to determine blood Rh factor

  - Access to medical facilities equipped to provide emergency care should that become necessary.

In this same letter they will also be asked to indicate their agreement to:

- Obtain signed acknowledgment from the patient that they have been provided with the product label, that they have read and understood the patient information, have had the procedure, its risks and benefits explained to them, and that they agree to follow the treatment procedure.

- Place the dose # on the acknowlegement and in the patient record.

- Maintain complete records for each patient including blood tests, ultrasound examinations and progress noted.

- Fill out and return AE (Adverse Event) cards to the distributor, identifying patient by dose # only.

- Use every effort to ensure patients return for their follow up visit 14-20 days after taking the product.